IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
ANDREW J. DANNENBERG.) Group Art Unit: 1617
)
Patent Application No. 09/554,604) Examiner: S. Wang
)
Filed: May 31, 2000)
)
For: CYCLOOXYGENASE-2 INHIBITION)

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REPLY BRIEF ON APPEAL (Three copies)

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is a Reply Brief on Appeal in the above-identified application.

1. (X) An Oral Hearing is requested.

2. ( ) An Oral Hearing is requested on _____.

3. ( ) An extension of time for filing the Brief on Appeal
( ) is hereby requested.
( ) was requested on _____.

4. (X) This application is entitled to small entity status.

The Appeal fee is calculated as follows:

	Large Entity	Small Entity	Amount
Notice of Appeal	$320.00	$160.00	
Request for Oral Hearing	280.00	140.00	$140.00
Request for Extension of Time for Filing Notice for Appeal			
( ) 1 month	110.00	55.00	
( ) 2 months	400.00	200.00	
( ) 3 months	920.00	460.00	
( ) 4 months	1,440.00	720.00	
( ) 5 months	1,960.00	980.00	
		TOTAL DUE $	140.00

5. ( ) No fee required.

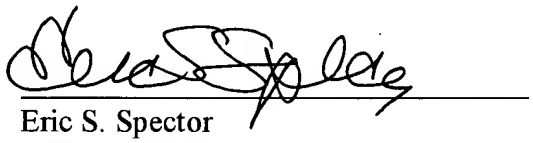
6. (X) A check in the amount of $140.00 is enclosed.
(Check No.17481)

7. ( ) Please charge Deposit Account No. 10-1213 in the amount of $_____. A duplicate of this sheet is enclosed.

8. (X) The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayment to Deposit Account No. 10-1213. A duplicate of this sheet is enclosed.

(X) Any patent application processing fees under 37 CFR 1.17.
(X) Any filing fees under 37 CFR 1.16. for presentation of extra claims.

Respectfully submitted,



Eric S. Spector
Reg. No. 22,495

Date: November 7, 2002

JONES, TULLAR & COOPER, P.C.
P.O. Box 2266 Eads Station
Arlington, VA 22202
703-415-1500

Case: CRF D-2165

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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ANDREW J. DANNENBERG.	)	Group Art Unit: 1617
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REPLY BRIEF ON APPEAL PURSUANT TO 37 C.F.R. 1.193 (b)(1)
(In Triplicate)

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This reply brief is in response to the Examiner's Answer of October 8, 2002.

Please consider the following:

There are two major errors in the positions in the Examiner's Answer supporting the rejection under 35 U.S.C. 103.

We turn now to the first major error in the Examiner Answer. The Examiner's Answer admits that it is relying only on Gregory for a position that COX-2 inhibitors are generally known for treating inflammatory disease (so it would be obvious from Gregory to treat alcoholic hepatitis which is an inflammatory disease), and are known for treating the liver diseases embraced by the term biliary cirrhosis and to reduce rejection in the case of liver transplant. This is a major error because 35 U.S.C. 103 requires that the subject matter as a whole be obvious, and the Examiner's Answer fails to properly consider the subject matter as a whole. In other words, the position in the Examiner's Answer ignores a basic tenet of patent law in an attempt to make a case.

{fee on transmittal}

In applying 35 U.S.C. 103, the differences between the subject matter to be patented and the prior art are assessed and a determination is made whether the subject matter as a whole is obvious. Note that the subject matter to be patented is treatment of any of four liver conditions different from any specific condition that Gregory teaches. The subject matter to be patented is directed to treating a patient affected with chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis. Gregory mentions as liver conditions only biliary cirrhosis and liver transplant (Gregory does not mention alcoholic hepatitis as the Examiner's Answer implies). The disorders set forth in applicant's claims are different from the specific liver disorders mentioned in Gregory et al as will be evident from discussion below of the second major error in the Examiner's Answer. Having determined the differences, the assessor of patentability must determine whether the differences are such that the subject matter as a whole would be obvious. In making this determination, one skilled in the art does not consider the applied prior art in a vacuum but rather needs to look at what else is relevant besides the applied prior art. In this case as discussed at page 9 of the Appeal Brief, quotations from the PDR indicate that even currently COX-2 indicators are considered to be counterindicated in the case of moderate hepatic insufficiency and in the case of clinical signs and symptoms of liver disease. Moreover, as indicated at page 5 of the Appeal Brief, at the time the invention was made, COX-2 inhibitors were not considered to be generally useful for treating inflammatory disorders.

This provides evidence that COX-2 is suitable for liver disorders.

In view of the subject matter as a whole as described above, it is submitted that the differences between the subject matter sought to be patented and the applied prior art are unobviousness.

The second major error in the Examiner's Answer is a new position (not previously articulated in any rejection or advisory action) and is really an anticipation position. The new position is that the "biliary cirrhosis" recited in Gregory meets the term "alcoholic liver injury" in Claim 3. The Examiner's Answer implies that secondary biliary cirrhosis embraces alcoholic cirrhosis and therefore meets the alcoholic liver injury of the claims. The new position is unsupported in the Examiner's Answer. Merck Manual (Home Edition) cited in the Examiner's Answer does not support the new position. The new position is egregiously incorrect. The new position appears to have been concocted in an attempt to revive the defective obviousness position described above.

the examiner merely argues that biliary cirrhosis is a species of cirrhosis, and is closely related to other cirrhosis.

Cirrhosis is a general term indicating a progressing liver condition. The progression of the cirrhosis is mediated by the cause of the cirrhosis which is typically indicated by a modifier preceding the term "cirrhosis". As indicated in the patent application herein at page 2, treatment is to delay the progression of the cirrhosis. The objective is to delay or stop the progression of cirrhosis so that it does not become end stage liver disease. Typically, different causes of cirrhosis call for different treatments to stop its progression.

Any liver doctor would agree that the biliary cirrhosis mentioned by Gregory is different from alcoholic cirrhosis and is different from the conditions treated in Claim 3, i.e., biliary cirrhosis is different from chronic viral hepatitis B, chronic hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis. The Examiner's Answer seems to admit that primary biliary cirrhosis is different from the conditions recited in Claim 3. The suggestion in the Examiner's Answer that the cirrhosis from alcohol ingestion is secondary biliary cirrhosis is dead wrong. Secondary biliary cirrhosis is a very uncommon condition that is a consequence of prolonged biliary outflow

obstruction. For example, an unrecognized biliary stricture leading to an efflux problem can cause secondary biliary cirrhosis. See Jeng, K.-S., et al Arch Surg 124, 1301-1305 (11/99) and Huizinga, U.K., et al, Annals of the Royal College of Surgeons of England 74, 119-125 (1992), copies enclosed.

Biliary cirrhosis, whether primary or secondary, is mediated by obstruction of bile ducts. Alcoholic cirrhosis is not mediated by obstruction of bile ducts but rather by alcohol ingestion.

The progression of biliary cirrhosis (mentioned in Gregory) would have to be inhibited by COX-2 inhibitors by amelioration of bile duct obstruction. Alcoholic cirrhosis does not involve bile duct obstruction. The only known treatment for alcoholic cirrhosis heretofore has been abstention from alcohol.

In view of the above, it is submitted that treatment of the disorders in the claims herein is not obvious from the treatment of the very different biliary cirrhosis recited in Gregory.

Request

It is requested that the decision finally rejecting Claims 3-5 and 17 be reversed.

Respectfully submitted,

JONES, TULLAR & COOPER, P.C.

By: _____

Eric S. Spector
Reg. No. 22,495

JONES, TULLAR & COOPER, P.C.
P.O. Box 2266 Eads Station
Arlington, Virginia 22202
703-415-1500

Case: CRF D-2165

Date: November 7, 2002

Secondary Biliary Cirrhosis

A Limiting Factor in the Treatment of Hepatolithiasis

Kuo-Shyang Jeng, MD; Shou-Chuan Shih, MD; Hsein-Jar Chiang, MD; Bee-Fong Chen, MD

• **To investigate whether the coexistence of secondary biliary cirrhosis plays a limiting role in the treatment of hepatolithiasis, we retrospectively compared the clinical course and results of stone treatment in 30 patients with secondary biliary cirrhosis (8 in Child's class A and 22 in Child's class B) (group 1) and 240 patients with noncirrhotic biliary calculi (group 2). The hospital mortality, morbidity of treatment, mortality of treatment, and the percentage of treatment failure in group 1 were 20%, 40%, 6.7%, and 16.7%, respectively. Those in group 2 were 8%, 10%, 3.8%, and 10%, respectively. The modes of treatment for stone removal included surgery with postoperative cholangioscopy and percutaneous transhepatic cholangioscopy. There was a statistically significant difference between these two groups in the hospital mortality and the morbidity of treatment. We conclude that hepatolithiasis and biliary stricture should be treated early, before the development of secondary biliary cirrhosis. However, even after cirrhosis occurs, aggressive treatment does not increase the mortality of treatment or the treatment failure rate.**

(*Arch Surg.* 1989;124:1301-1305)

Hepatolithiasis occurs with a high incidence in Asia. Among Asian countries, Taiwan has the highest relative prevalence of patients with gallstones undergoing biliary surgery.[1,2] In the treatment of hepatolithiasis, surgery with postoperative choledochoscopy through the choledochal T-tube track was the usual mode of therapy.[3-10] Percutaneous transhepatic cholangioscopy (PTCS) has been accepted as an alternative to avoid repeated surgery,[5,11,12] especially in poor-risk patients, in those with residual or recurrent calculi, and in those with a history of multiple biliary surgical procedures. However, biliary stricture, intrahepatic ductal angulation, and biliary sepsis are well-known problems that may result in treatment failure.

Secondary biliary cirrhosis that develops after a long period of biliary stricture, calculous obstruction, and repeated cholangitis[13-15] may lead to hepatic insufficiency and portal hypertension with the resultant complications, ie, bleeding esophageal varices, hypersplenism with pancytopenia, ascites, and encephalopathy. The influence of secondary biliary cirrhosis on the treatment of hepatolithiasis has not been clearly studied. To investigate the role of the coexistence of secondary biliary cirrhosis in the management of calculi, we conducted a retrospective study of 298 patients with hepatolithiasis.

PATIENTS AND METHODS

From July 1985 through February 1988, a total of 298 patients with hepatolithiasis received surgical treatment at Mackay Memorial Hospital, Taipei, Taiwan. The treatment in these 298 patients consisted of a total of 310 operations, 942 sessions of postoperative choledochoscopy through the matured choledochal T-tube track for removal of residual calculi, and 124 consecutive sessions of PTCS lithotomy in 50 patients with complicated biliary calculi. The indications for PTCS lithotomy included history of multiple biliary operations and recurrent or residual calculi that could not be removed by surgery or conventional postoperative choledochoscopy. To establish the liver abnormality, a wedge biopsy of liver was routinely undertaken during each exploration.

Secondary biliary cirrhosis was defined by both a history of biliary calculi with cholangitis for more than 5 years and confirmed pathologic findings of portal-portal linkages, with a pattern of monolobular cirrhosis, and the absence of normal vascular relationships (Fig 1). Thirty patients fulfilled the criteria; there were 15 men and 15 women, ranging in age from 25 to 71 years (mean, 46.4 ± 2.9 years). They were denoted group 1. Child's classification of liver function was class A in 8 patients and class B in 22 patients (normal prothrombin time and platelet count greater than 80×10^9/L).

Among the other 268 patients with hepatolithiasis, 28 patients were excluded from this study because of the pathologic findings of undefined subcapsular fibrosis, undefined causes of cirrhosis, alcoholic liver cirrhosis, postnecrotic (hepatitis) liver cirrhosis, primary biliary cirrhosis, choledochal cysts, and the coexistence of hepatocellular carcinoma or metastatic colorectal cancer. The remaining 240 patients who were noncirrhotic consisted of 109 men and 131 women, who ranged in age from 19 to 92 years (mean, 48.3 ± 19.5 years). They were denoted group 2.

The locations of biliary calculi and the sites of biliary stricture of all patients were classified by the intrahepatic and extrahepatic hepatolithiasis (IE) system proposed by the Research Group for the Study of Damage to the Intrahepatic Bile Duct from Japan[16] on the basis of the preoperative cholangiogram. In both groups 1 and 2, all patients received extended intrahepatic choledocholithotomy and operative cholangioscopy, cholecystectomy if the gallbladder was present, and left lateral segmentectomy or left lobectomy of the liver if left intrahepatic stones or left hilar biliary stricture was found. The postoperative choledochoscopy through the matured T-tube track to remove the residual stones was performed routinely and was repeated until the stones were completely eradicated or failure was concluded by means of this technique. The number of sessions varied from one to

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From the Departments of Surgery (Dr Jeng), Gastroenterology (Dr Shih), Radiology (Dr Chiang), and Pathology (Dr Chen), Mackay Memorial Hospital, Taipei City, Taiwan.

Reprint requests to Department of Surgery, Mackay Memorial Hospital, No. 92, Section 2, Chung-Shan North Road, Taipei City, Taiwan 10449, Republic of China (Dr Jeng).

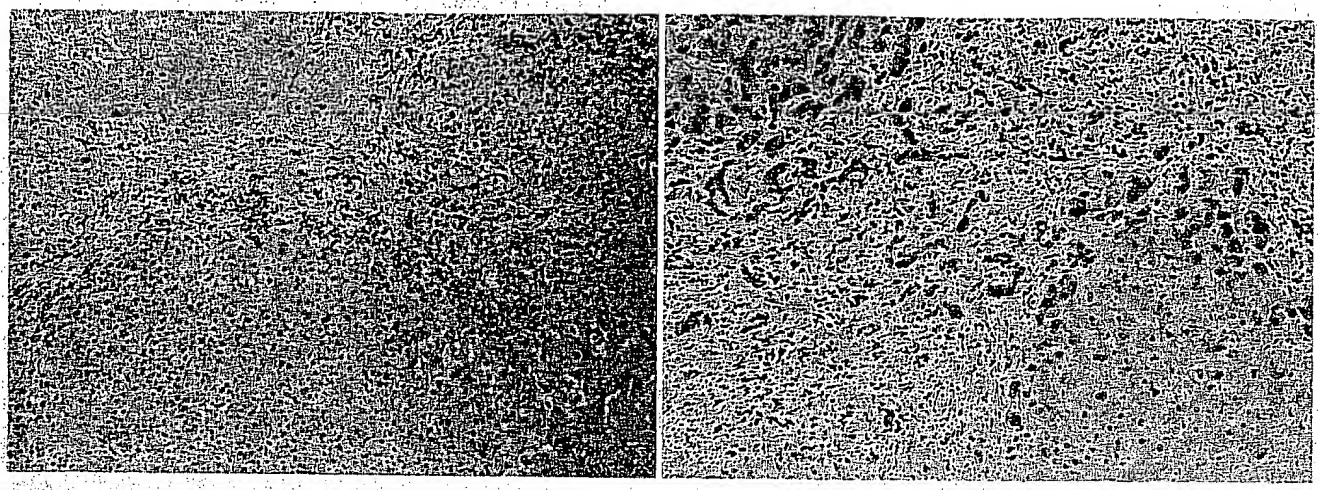

Fig 1.—Left, Liver biopsy specimen shows broad fibrous septa producing a puzzlelike appearance (hematoxylin-eosin, ×40). Right, The broad fibrous septa show prominent bile duct proliferation with bile plugs and chronic inflammatory infiltrate (hematoxylin-eosin, ×100).

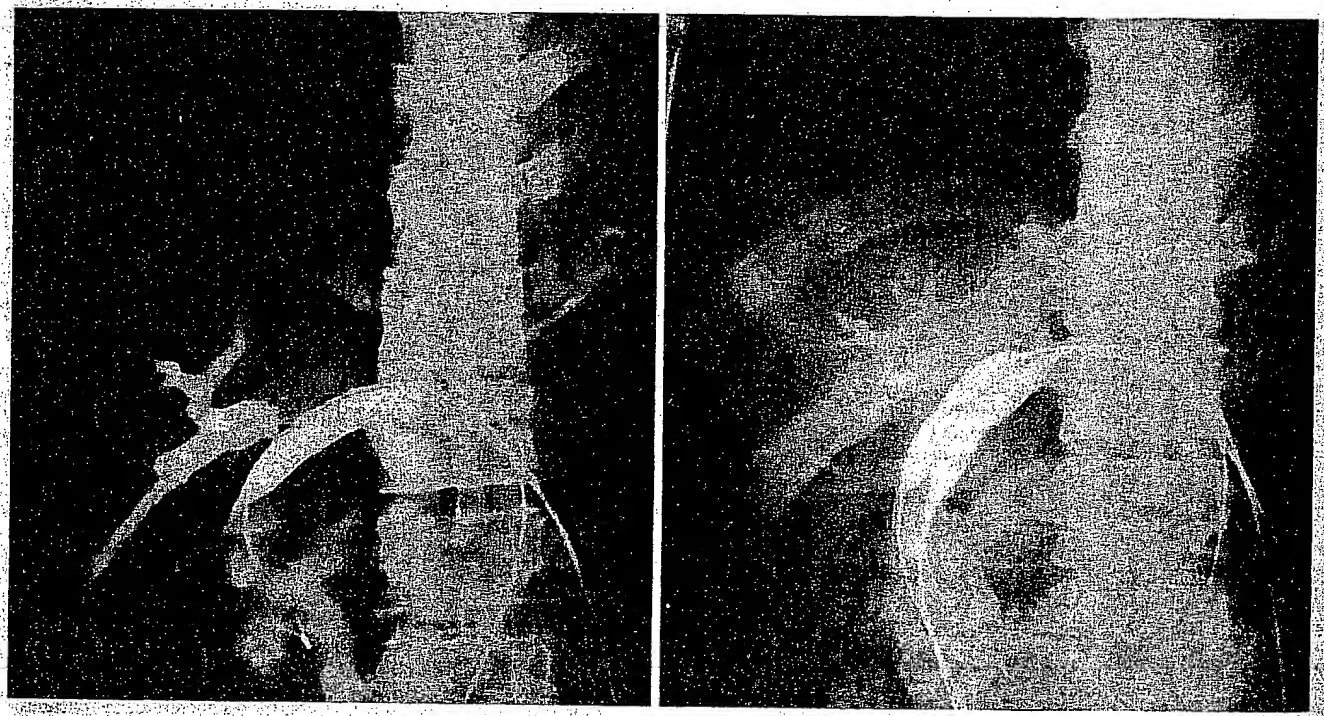

Fig 2.—Left, During percutaneous transhepatic cholangioscopic lithotomy, one balloon Dotter dilator is used for dilation of intrahepatic biliary stricture. Right, Increment of dilation is done with a two-balloon dilator.

nine per patient, depending on the biliary conditions. Percutaneous transhepatic cholangioscopy was undertaken in 50 selected patients who had severe biliary stricture or whose retained calculi were complicated and could not be removed by the usual procedures of surgery and the postoperative choledochoscopy. The technique included percutaneous track establishment by PTCS, track dilations by balloon dilators (Fig 2), and repeated cholangioscopy. The overall percutaneous manipulations consisted of 221 procedures, including 124 sessions of PTCS. In each patient, the number of sessions of PTCS varied from one to seven. In selected cases, on PTCS, electrohydraulic lithotripsy for stone fragmentation, biliary spoons, grasping forceps, and flushing technique for stone retrieval were added as an adjunct to basket catheters. Reoperations were undertaken in 12 patients because of inadequacy of the initial operation or complications developing from the initial surgery or the failure of PTCS treatment.

Every procedure and any complication, either minor or major, occurring during or after each procedure in each patient were recorded in as much detail as possible. The assessment of complete removal of complicated stones was evaluated visually by cholangioscopy at the end of treatment, by cholangiography performed repeatedly through the T-tube tract or the PTCS sinus tract, and by abdominal ultrasonography (real time, 3.5 MHz, Aloka, SSD 256, Tokyo, Japan), which was routinely performed every week during the stone therapy. The cause of every treatment failure was investigated. To compare the clinical course and the treatment result between groups 1 and 2, the hospital mortality, the morbidity of treatment, the mortality of treatment, and the rate of treatment failure in stone removal in both groups were evaluated.

Hospital mortality included both the mortality related to treatment and the disease mortality. The deaths that were mainly attributable to surgery or PTCS, such as postoperative intra-abdominal

Results of Comparison of Groups 1 and 2

	Hospital Mortality	Mortality of Treatment	Morbidity of Treatment	Treatment Failure (Residual Stones)
Secondary biliary cirrhosis (n=30), No. (%)	6 (20)	2 (6.7)	12 (40)	5 (16.7)
Noncirrhotic biliary calculi (n=240), No. (%)	18 (7.5)	8 (3.3)	24 (10)	24 (10)
P (χ^2 test)	<.04	>.05	<.002	>.05

hemorrhage or abscess, postoperative respiratory failure, or unstable diabetes, were included in the "mortality of treatment." The deaths relating to the disease process of hepatolithiasis or biliary cirrhosis, such as suppurative cholangitis, concomitant acute pancreatitis, esophageal variceal bleeding, or hepatic failure, were included in the "disease mortality." When the morbidity (complications) of treatment was discussed, the mortality cases were excluded. "Treatment failure" was defined as the persistence of residual stones at the end or discontinuation of treatment.

RESULTS

In group 1, there were six hospital deaths (hospital mortality, 20%), including two surgical deaths and four disease deaths. Both surgical deaths (mortality of treatment, 6.7%) were attributed to postoperative intra-abdominal sepsis after hepatectomy. These patients had left hepatic hilar biliary stricture, left hepatic calculi, suppurative cholangitis, and coexistent secondary biliary cirrhosis. The causes of death in the other four patients (included in the disease mortality) consisted of intractable upper gastrointestinal tract bleeding from ruptured esophageal varices in one and hepatocellular failure with hepatic coma in three. All deaths were related to the sequelae of secondary biliary cirrhosis. All six patients with hospital deaths were in Child's class B.

Complications of treatment for calculi occurred in 12 patients in group 1 (morbidity of treatment, 40%). Those after surgery included wound infection in 1 patient, intra-abdominal abscess in 1, hepatocutaneous fistula in 1, ventral hernia in 1, and stress ulcer with gastrointestinal tract hemorrhage in 1. Those after PTCS consisted of massive hemobilia in 5 patients and pain intolerance in 2 patients.

Among the seven patients who had complications after PTCS therapy, the locations of biliary strictures and calculi were distributed in the left hepatic hilum in four patients, in the right hepatic hilum in one patient, in the periphery (multiple) in one patient, and in the bilateral hepatic hilum with right hepatic periphery in one patient. Massive hemobilia was stopped successfully by transcatheter hepatic arterial embolization in three patients (two on the right and one on the left), by intraarterial (right) catheter vasopressin (Pitressin) drip in one patient, and by transhepatic intraductal balloon-dilator compression in another patient. One patient with pain intolerance and one with massive hemobilia gave up further stone treatment. Reoperations were undertaken in one patient for the repair of ventral hernia and in two patients for hepatectomy after the failure of PTCS. Conservative treatment was successful in patients with fistula, stress ulcer bleeding, and wound infections.

In group 2, hospital mortality was 7.5% (18/240), which included 7 patients (3.3%) with treatment-related deaths and 11 patients with disease-related deaths. The cause of death related to the original disease process was severe cholangitis and uncontrollable sepsis in 8 patients and concomitant acute pancreatitis in 3 patients. The treatment mortality was attributed to postoperative unstable diabetes and hyperglycemic hyperosmolarity nonketoacidosis in 1 patient, postoperative hemorrhage in 1 patient, postoperative intra-abdominal abscess in 2 patients, sepsis with respiratory distress after failure of PTCS therapy in 2 patients, and death after complications of general anesthesia in 1 patient. The morbidity of treatment in group 2, 10% (24/240), included wound infection or wound sepsis (12 patients), minor bleeding during PTCS therapy (2 patients), pain intolerance during PTCS therapy (2 patients), slipping out of the choledochal T tube (3 patients), pneumonia (1 patient), intra-abdominal sepsis (1 patient), postoperative ventral hernia (2 patients), and stricture of hepatojejunostomy (1 patient).

Five (16.7%) of 30 patients in group 1 and 24 (10%) of 240 patients in group 2 failed to achieve complete clearance of hepatolithiasis. In group 1, 2 patients gave up further treatment because of pain intolerance and hemobilia during PTCS and 3 patients could not receive continuing stone removal because they died of their disease. The reasons for discontinuation of stone treatment were death from disease in 11 patients, treatment-related death in 7 patients, patients deciding to stop treatment in 5, and the surgeon deciding to stop treatment in 1. The 5 patients who decided against further trial of stone clearance did so because of the development of complications such as pain intolerance, hemobilia, and dislodgement of the T tube. The surgeon discontinued the treatment in 1 patient because of pneumonia. The rate of and reasons for treatment failure in both groups were similar.

From χ^2 testing, there were statistically significant differences between groups 1 and 2 in hospital mortality ($P<.04$) and morbidity of treatment ($P<.002$). However, no significant differences in mortality of treatment ($P>.05$) and rate of treatment failure for calculi ($P>.05$) were noted (Table).

COMMENT

Failure to relieve mechanical obstruction of bile outflow may lead to secondary biliary cirrhosis.[17] The rate of evolution of a true cirrhosis is variable. The degree of mechanical obstruction to bile outflow and the occurrence of cholangitis determine its course. In adults, it has been estimated that secondary biliary cirrhosis develops some 7 years after the onset of obstruction from a stricture, 4.5 years after a calculous obstruction, and 10 months after the onset of a malignant stricture.[18] In some diseases, which initially are focal within the liver, the evolution of a true cirrhosis takes place over a period that extends to 15 years or more.

The incidence of secondary biliary cirrhosis in hepatolithiasis in our series was about 10.1% (30/298). It is well known that there is a better prognosis and a greater practicability of aggressive management in those with Child's class A than in those with Child's class B or C. In our series, all causes of death and major complications in group 1, such as esophageal variceal bleeding, hepatic failure, postoperative intra-abdominal sepsis, and massive hemobilia, occurred in patients in Child's class B. Their mortality was as high as 20%, including a 13.3% disease mortality and a 6.7% treatment mortality. The patients in Child's class A had only minor complications.

In group 2, the main causes of death unrelated to surgery or PTCS for calculi were suppurative cholangitis with resultant

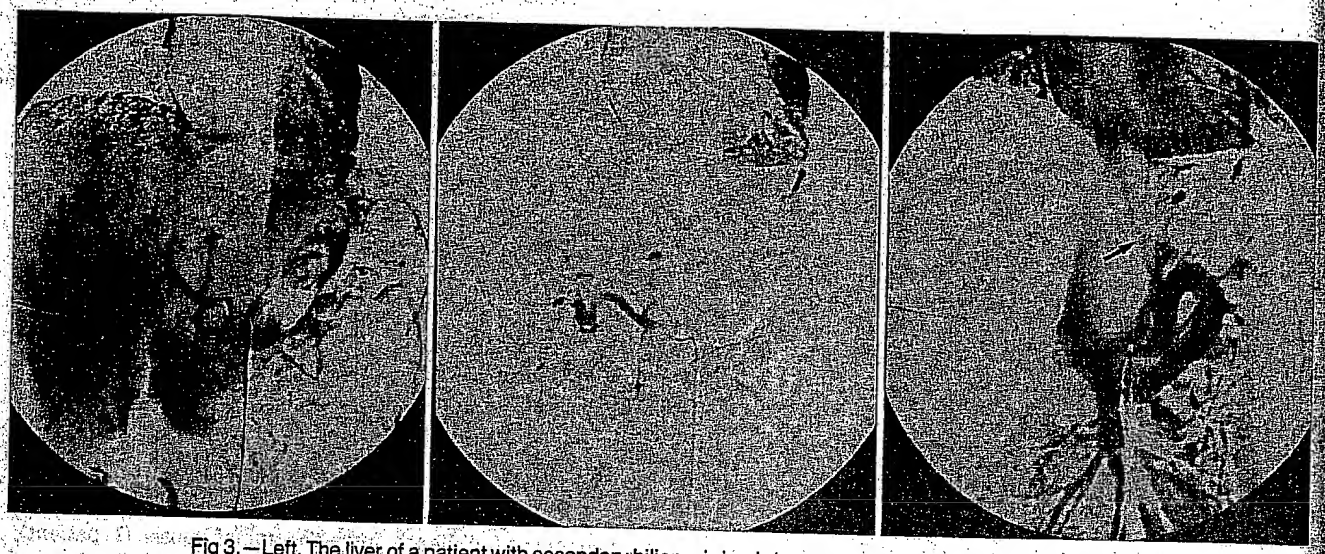

Fig 3.—Left, The liver of a patient with secondary biliary cirrhosis becomes mainly fed by hepatic arteries instead of portal vein (heavy hepatogram). Center, The corkscrew appearance of the patient's hepatic arteriogram is related to secondary biliary cirrhosis. Right, The venous phase of the superior mesenteric angiogram shows a patent splenorenal shunt and nonvisualization of the portal vein. The esophageal varices resulting from secondary biliary cirrhosis are noted (arrow).

uncontrollable sepsis and multiple organ failure. The timing of treatment influenced the prognosis. A delay in diagnosis and treatment made septic shock and death irreversible. Three patients were victims of acute biliary pancreatitis. Two died of necrotizing pancreatitis and 1 died of pancreatic abscess without early treatment. Intra-abdominal sepsis occurred in 10% (3/30), with 2 deaths, in group 1 and 1.3% (3/240), also with 2 deaths, in group 2 (10% vs 1.3%, $P<.05$). Patients with secondary biliary cirrhosis may be prone to the development of postoperative sepsis.

Among the scope of postprocedural complications, wound infection occurred in half of the cases (12 of 24) of morbidity of group 2, while little wound infection was found in group 1. The reason may be attributed to the large numbers receiving surgery in group 2 compared with the small number of patients in group 1. All the wound infections improved after conservative treatment and meticulous wound care. Other surgical complications, such as stricture of the bilioenteric bypass in 1 case and slipping out of the choledochal T tube in 3 cases, occurred during the postoperative therapy with choledochoscopy. Pain intolerance was one of the main complications of PTCS therapy. Pain was experienced by the majority of patients undergoing PTCS therapy because most procedures were performed with local anesthesia. However, these patients were included in the complication category of pain intolerance only when they gave up PTCS therapy for this reason. They suffered pain especially on skin puncturing when the PTCD track was established, stone crushing by the adjunct of electrohydraulic lithotripsy, repeated stricture dilating by balloon dilators, and stone extracting or grasping by biliary basket catheters.

There were two options for the patients who gave up further PTCS therapy. One was for them to continue therapy with reoperation, mainly left hepatectomy, especially when the retained calculi or biliary stricture were present in the left side of the liver. The other option was to give up any treatment procedure and be discharged with the retained calculi. The latter patients were included in the treatment failure group.

We emphasize the complications of massive bleeding during PTCS therapy in group 1. Bleeding is another major complication of PTCS, especially on the establishment of the PTCD track or the dilatation of the biliary stricture. However, bleeding was minor in group 2. Massive bleeding, which is defined as a blood loss of more than 1000 mL, occurred only in group 1. The reasons and sites of bleeding were investigated in as much detail as possible in the five patients in whom massive bleeding occurred. Each of the five patients had coexistent secondary biliary cirrhosis with liver reserve of Child's class B. Emergency angiography was undertaken at the onset of massive hemobilia during PTCS. Neovascularization surrounding the stenotic hepatic duct from the proliferation of the bile duct in the cirrhotic process, which has been described by Buyssens,[19] was demonstrated on the liver computed tomographic scans in two of our patients. A pseudoaneurysm of the right hepatic artery that formed after intimal injury following repeated PTCS manipulation was detected in one patient. Another young female patient's angiogram demonstrated the so-called heavy hepatogram, which means that the blood supply to the liver was mainly from the hepatic artery instead of the portal vein (Fig 3). She had received splenorenal shunt surgery in the past because of the intractable bleeding from the ruptured esphageal varices that occurred as an end sequel of her secondary biliary cirrhosis with portal hypertension. The hepatogram increased her vulnerability to bleeding during the manipulations of PTCS therapy. Previous shunt surgery was an important contributing factor to her bleeding during PTCS therapy.

The contributing factors other than cirrhosis in the fifth victim of massive hemobilia consisted of severe multiple intrahepatic biliary stricture, anomalous accessory hepatic duct, and the coexistence of intrahepatic ductal cholangiocarcinoma. He received chest tube intubation and computed tomographic scan–guided percutaneous transhepatic drainage of hematoma within his liver. Bleeding was controlled after these conservative manipulations. Though no residual calculi remained within his liver at the end of all treatment, he died of hepatic failure and coexistent cholangiocarcinoma.

As is the case in postnecrotic or alcoholic liver cirrhosis, abnormal intrahepatic anastomoses exist in patients with secondary biliary cirrhosis. Abnormal intrahepatic anastomoses have been shown to exist between the portal and the hepatic veins, between the hepatic artery and the hepatic vein, and between the hepatic artery and the portal vein.[20-30]

The existence of such intrahepatic shunts of quantitative importance between the hepatic artery and hepatic vein may have special significance in cirrhotic patients who already have diminished portal flow, particularly in patients with bleeding varices who are candidates for shunt operation, which would further deprive the liver of its portal flow. The main blood supply to the liver of such patients after shunt surgery would be from the hepatic artery. Blood transfusion was necessary in our five patients with massive hemobilia. Therapy with PTCS for calculi was postponed or delayed once the complications occurred. Massive hemobilia became a significant cause of morbidity in patients in group 1. The vulnerability to bleeding is an important limitation of stone treatment because of the increased morbidity and the increased rate of treatment failure. However, hemolibia also developed during the stone treatment, especially during PTCS therapy, in patients in group 2, even though their bleeding was relatively minor and there was no necessity for blood replacement.

The other significant difference between groups 1 and 2 was the disease mortality. The main cause was that end-stage liver disease leading to variceal bleeding or hepatic failure with encephalopathy occurred in those with advanced secondary biliary cirrhosis; it is a sequela of cirrhosis and is also an important limitation during stone therapy.

Compared with the noncirrhotic patients with hepatolithiasis, the cirrhotics had more postprocedural complications. They did not, however, have higher mortality as a result of the treatment and could achieve the same stone clearance rate. We conclude that early diagnosis and complete treatment of hepatolithiasis to prevent the development of secondary biliary cirrhosis is mandatory. Though secondary biliary cirrhosis plays a significant role in the limitation of treatment of hepatolithiasis because of the sequelae of cirrhosis and the vulnerability to bleeding, active management of stones in symptomatic patients is still advocated.

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Chronic pancreatitis with biliary obstruction

William K J Huizinga MD FRCSEd
Consultant Surgeon

Jean-Marie Spitaels MD
Consultant Physician

Sandie R Thomson ChM FRCS
Consultant Surgeon

Ahmed E Simjee FRCP
Associate Professor of Medicine

Department of Surgery and Gastro-Intestinal Unit, Natal University Medical School, Durban, South Africa

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In a 4-year review of 509 patients with chronic pancreatitis, the incidence of clinically manifest fixed common bile duct (CBD) stenosis was 9% (45 patients). In 76% this was alcohol related, and pancreatic calcification was present in 51%. All patients presented with unrelenting jaundice and five (11%) had cholangitis. The mean serum bilirubin (165 ± 108, normal 0–17 μmol/l), alkaline phosphatase (1790 ± 1143, normal 73–207 U/l) and gamma glutamyl transferase (798 ± 660, normal 7–64 U/l) were markedly raised. Diabetes occurred in 8 (18%). A biliary drainage operation was performed in 43 patients and 11 had concomitant pancreaticojejunostomy. Endoscopic retrograde cholangiopancreatography (ECRP) provided valuable information preoperatively in outlining both biliary and pancreatic disease in selecting patients for dual ductal drainage. Minor complications not related to biliary anastomosis occurred in 14%. Four patients died (9%), two from pseudocyst-related haemorrhage. Jaundice was successfully relieved in all and did not recur during follow-up. No secondary biliary cirrhosis was encountered, but varying degrees of portal fibrosis were present in 75% of liver biopsies. The commonest biliary pathogen was *E. coli*. It is recommended that a biliary bypass operation be performed when the diagnosis is radiologically confirmed and no improvement occurs within 1 month.

Chronic pancreatitis is usually due to excess alcohol intake. Some other conditions may contribute, such as hypercalcaemia, hyperlipidaemia, pancreatic trauma and congenital pancreatic abnormalities. Biliary tract disease rarely causes chronic pancreatitis. In alcoholic pancreatitis, deposition of proteinaceous material within the acini and ductules results in glandular destruction and replacement with fibrous tissue. The main pancreatic duct becomes distorted with varying degrees of narrowing, tortuosity and dilatation. Progressive damage to the gland eventually leads to loss of exocrine and endocrine function. Chronic inflammation and scarring may also involve nearby structures such as duodenum, colon and common bile duct. The latter is especially at risk as it traverses the pancreatic head for some distance.

Stenosis of the distal common bile duct in chronic pancreatitis is reported to occur from as low as 3% to as high as 62% *(1–9)*. The precise indications for biliary drainage and its timing are unclear. We reviewed our recent experience with this complication.

Patients and methods

The records of 509 patients with a final diagnosis of chronic pancreatitis admitted during the 4-year period 1986–1989 at King Edward VIII Hospital, Durban, were reviewed. The diagnosis was on the basis of information obtained by plain abdominal radiographs, ultrasonography, ERCP, CT-scanning, pancreatic function tests, operative findings or biopsy material. A total of 45 patients presented with unrelenting jaundice due to fixed stenosis of the distal common bile duct, an incidence of 9%. They form the basis of this analysis.

Sex and ag

There were 38 males and 7 females with a median age of 39 years (range 25–80 years).

Correspondence to: Mr W K J Huizinga, Department of Surgery, Natal University Medical School, Durban, PO Box 17039, Congella 4013, South Africa

Table I. Presenting signs and sympt[redacted] ($n = 45$)

	n	%
Pain	43	95.6
Jaundice	45	100.0
Hepatomegaly	33	73.3
Abdominal tenderness	27	60.0
Malaise, vomiting	21	46.7
Malnutrition	16	35.6
Pruritus	15	33.3
Abdominal mass	8	17.8
Fever	5	11.1

Symptoms and signs

The usual presentation was with upper abdominal pains and jaundice and in one-third to one-half of the patients malaise, vomiting and pruritus. Most had epigastric tenderness and hepatomegaly on physical examination. Five patients (11%) had a fever and eight (18%) an abdominal mass (Table I). Twenty-three patients had previously been admitted with pancreatitis on one or more occasions. A relationship with alcohol consumption was present in 34 (76%), malnutrition occurred in 16 (36%) and diabetes in 8 (18%) of the patients. Pancreatic calcification was demonstrated in 23 (51%).

Laboratory results

The mean total serum bilirubin (165 ± 108 μmol/l), alkaline phosphatase (1790 ± 1143 U/l) and gamma glutamyl transferase (GGT, 798 ± 660 U/l) were markedly raised. The mean serum levels of aspartate transaminase (AST), alanine transaminase (ALT), lactic dehydrogenase (LDH), amylase and albumin were near normal and so were the international ratio of prothrombin time (INR) and partial thromboplastin time (PTT) (Table II).

Table II. Laboratory results

	Mean ± SD	*Distribution*	*Reference range*
Bilirubin	165 ± 108	>50: $n=40$ >100: $n=30$	0–17 μmol/l
Alk.phos	1790 ± 1143	>500: $n=40$ >1000: $n=32$	73–207 U/l
GGT	798 ± 660	>500: $n=27$ >1000: $n=10$	7–64 U/l
AST	111 ± 68		10–42 U/l
ALT	81 ± 71		10–60 U/l
LDH	302 ± 43		266–500 U/l
Amylase	233 ± 113		44–128 U/l
Albumin	30 ± 8.5		38–48 g/l
INR	1.13 ± 0.22		<1.2
PTT	33.4 ± 7.4		24–34 s

Alk.phos = Alkaline phosphatase
LDH = Lactic dehydrogenase
GGT = Gamma glutamyl transferase
AST = Aspartate transaminase
ALT = Alanine transaminase
INR = International ratio of prothrombin time
PTT = Partial thromboplastin time

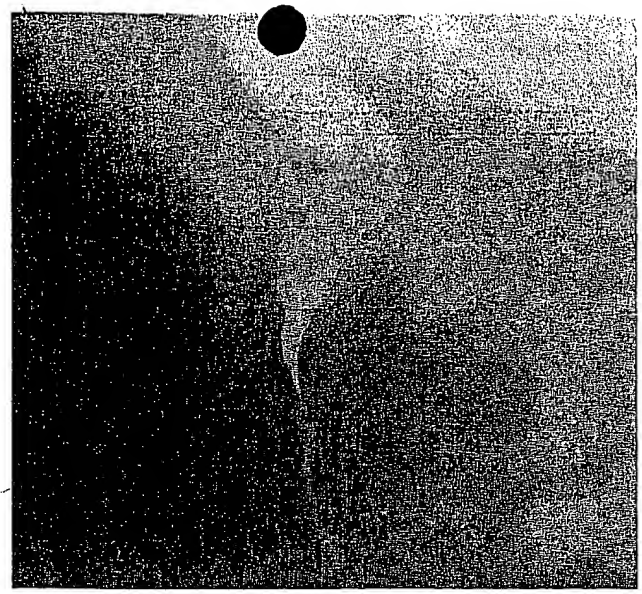

Figure 1. Smooth long stricture in the distal common bile duct, resulting from chronic pancreatitis. There is proximal dilatation of the bile duct. Note calcifications in the head of the pancreas.

Biliary-pancreatic imaging

The patients had a chest radiograph (pleural effusions present in five) and plain supine abdominal radiograph (pancreatic calcification present in 23) and all subsequently underwent ultrasonography, which demonstrated the features of extrahepatic biliary obstruction.

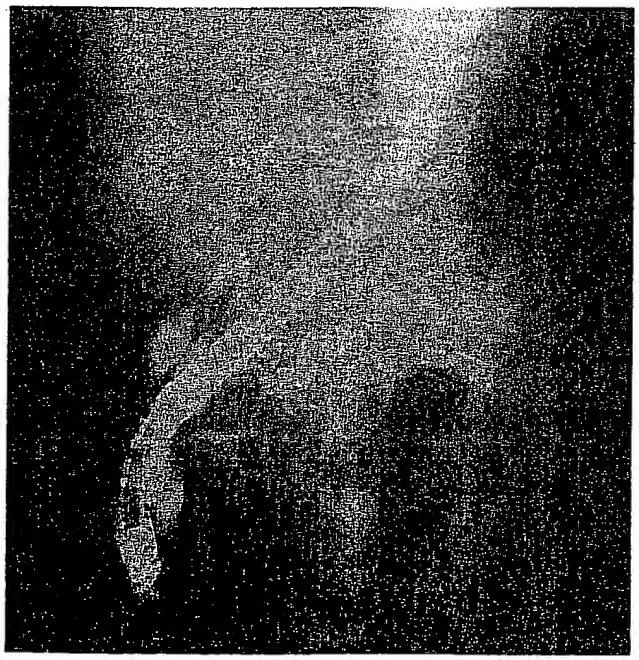

Figure 2. Chronic pancreatitis with ductal abnormalities, most obvious in the tortuous and dilated distal part.

Table III. ERCP findings ($n = 32$)

	n	%
Bile duct outlined (78%)	25	
Stenosis distal CBD	25	100
Dilated proximal CBD	20	80
Dilated IHBD	6	24
Dilated gallbladder	3	12
Stones	2	8
Pancreatic duct outlined (81%)	26	
Distorted MPD	19	73
Dilated MPD	16	62
Pseudocysts	5	19
Calcification	10	38

CBD = Common bile duct
IHBD = Intrahepatic bile duct
MPD = Main pancreatic duct

ERCP was performed in 32 patients and the bile duct was successfully cannulated in 25 (78%). A smooth stricture in the distal common bile duct related to the pancreas was present in all cases (Fig. 1). The pancreatic duct was outlined in 26 (81%) and main pancreatic duct dilatation demonstrated in 16 (62%) of these (Fig. 2). The ERCP findings are summarised in Table III. Where ERCP had been unsuccessful, a percutaneous transhepatic cholangiography (PTC) was carried out in nine patients, demonstrating a distal CBD stricture with proximal dilatation in them all. Preoperative CT scanning or a barium meal were obtained in 13 patients, while 19 underwent intraoperative cholangio- and/or pancreatography.

Operations (Table IV)

A total of 43 patients was operated on by various surgeons because of persistent jaundice. One of these patients had previously had a cholecystojejunostomy elsewhere. The two other patients declined operation. A biliary drainage procedure, most commonly a side-to-side choledochoduodenostomy was performed in 38 patients, and nine had internal or external drainage of a pseudocyst. In five of these, bile flow into the duodenum improved markedly as shown on intraoperative cholangiography and no further biliary drainage was undertaken. The other four patients required biliary drainage procedures. A cholecystectomy was performed in 20 instances. Eleven patients had a concomitant pancreaticojejunostomy for chronic pain associated with pancreatic duct dilatation on ERCP. Five patients had evidence of duodenal obstruction, for which a gastrojejunostomy was performed in three. Drainage of pseudocysts relieved the obstruction in the other two patients. One poorly nourished patient presented with an acute bleed into a pancreatic pseudocyst. For expediency and safety he was treated by arterial ligation within the pseudocyst, external tube drainage of the cyst and CBD decompression with a T-tube. He rebled in the intensive care unit and died. At operation, 22 patients had liver biopsies and 26 patients had pancreatic biopsies.

Table IV. Operations ($n = 43$)

Biliary drainage	
Choledochoduodenostomy	21
Choledochojejunostomy	4
Cholecystojejunostomy	12
Cholecystectomy	20
Choledochotomy + T-tube	1
Pancreatic drainage	
Pancreaticojejunostomy	11
Pseudocyst drainage	
Cyst–gastrostomy	4
Cyst–duodenostomy	2
External drainage	3

Results

All patients had their jaundice successfully relieved and there were no complications related to the biliary–digestive anastomosis.

Complications

Minor problems occurred in six patients (14%) and major in four, all resulting in death (9%). The causes of death were renal failure in a patient with pre-existing renal disease, haemorrhage from a cyst-gastrostomy on the 9th postoperative day, septicaemia after revision of a cholecystojejunostomy previously performed elsewhere, and uncontrollable haemorrhage from a false aneurysm related to the gastroduodenal artery. The average hospital stay was 25.9 (±15.7) days.

Histology

The 22 liver biopsies all showed evidence of large duct obstruction with widening of the portal tracts, bile duct proliferation, centrilobular cholestasis and mixed inflammatory infiltrates. Varying degrees of fibrosis, some with early bridging and cross-linking, were present in 16 patients (73%), but no definite secondary biliary cirrhosis was found. Cholangitis was present in three instances (14%). In all patients the appearances at operation suggested chronic pancreatitis, which was confirmed in all 26 pancreatic biopsies. No biopsies showed carcinoma. Chronic cholecystitis was present in 14 (70%) of the 20 gallbladders removed and acute cholecystitis in 3 (15%). Pigment stones were found in two.

Microbiology

Bile swabs from 36 patients yielded a variety of gut-associated organisms, most commonly *E. coli*, *Enterobact. cloacae* and *Strept. faecalis*. The only anaerobic organism isolated was *C. welchii*, and *Candida*

albicans was identified twice. Blood cultures were positive in two patients with cholangitis (*Str. pneumoniae* and *E. coli*). Organisms grown from pseudocyst collections were *Staph. aureus*, *Str. viridans* and *Klebsiella* sp.

Follow-up

Of the 39 patients who left hospital after operation, 26 (66.7%) were available for follow-up assessment, with a mean duration of 25.6 months. None developed recurrence of clinical obstructive jaundice. In addition to the four hospital deaths there were three late deaths. One patient died 3 months after a combined biliary and pancreatic drainage procedure with undiagnosed lower intestinal haemorrhage. Another died 8 months after operation with pneumonia on the basis of pre-existing pulmonary tuberculosis. He had no jaundice. One patient died after 1.5 years in liver failure with encephalopathy, ascites, portal hypertension and deep jaundice. At the initial operation the liver did not appear cirrhotic, but no information was available from histology or post-mortem. Two patients developed cholangitis 1.5 and 4 years, respectively, after a cholecystojejunostomy and were treated conservatively with antibiotics. After biliary drainage, nine patients had significant persistent pain in association with continued alcohol intake. Two patients underwent ERCP and a widened main pancreatic duct was demonstrated in both, one of whom underwent a pancreaticojejunostomy with good result. Seven patients returned for follow-up after their pancreaticojejunostomy and had marked pain relief. In the remaining patients pain was minimal or tolerable. Pseudocysts occurred in two patients with spontaneous resolution; diabetes and malabsorption developed in three and adhesive intestinal obstruction was treated non-operatively in another patient.

Discussion

The distal common bile duct is at risk of involvement in pancreatic disease due to its intrapancreatic course. Temporary narrowing of the duct may result from oedema in acute pancreatitis or compression by a pseudocyst, but on resolution of these conditions the bile duct reverts to normal. In chronic pancreatitis, scar tissue encroaches on to the distal common bile duct and renders it permanently stenosed with resultant bile flow obstruction. Not all patients with chronic pancreatitis and biliary obstruction present with jaundice. A rise in alkaline phosphatase may be found incidentally without unduly raised serum bilirubin. The significance of a chronically raised alkaline phosphatase and its influence on potential liver damage and attacks of cholangitis is not yet clearly established *(3–6,13)*. A recommendation has been made that patients with high alkaline phosphatase levels and pancreatitis should be followed up with liver biopsies twice a year to detect onset of secondary biliary cirrhosis *(4)*. The incidence of biliary stricture in chronic pancreatitis is estimated at 3–62% depending on the extent of diagnostic endeavour *(1–9)*. The incidence in our study was 9%. Although ethanol is pancreato-, as well as hepato-toxic, there was no documented alcoholic liver damage in any of our patients, although it was suspected in one who died on follow-up. Some patients may well respond primarily with pancreatic, and others with liver disease. Clark *(10)* found cirrhosis at autopsy in 17 (47%) of 36 patients with alcoholic pancreatitis and two other studies found biopsy proven alcoholic liver disease in chronic pancreatitis in 30% and 40%, respectively *(11,12)*. The end result of chronic pancreatitis is exocrine and endocrine insufficiency. Diabetes occurred in 18% of our patients, but the incidence may be as high as 50% *(13)*. Secondary biliary cirrhosis was not unequivocally present in any of our liver biopsies, but various degrees of portal triad fibrosis, with crosslinking around the central lobule in some, was seen frequently. The significance of this is unclear, but it may represent a prephase to cirrhotic change. The incidence of secondary biliary cirrhosis is generally thought to be low, from 0–10% *(1,3–5,7,8,13)*, and our findings are in agreement with this. The duration of biliary obstruction necessary to produce biliary cirrhosis is usually not clearly documented but is probably very important. The long-term effect of continuing bile duct obstruction cannot be assessed, since in 96% of our cases the obstruction was relieved by operation. Cholangitis is another potential complication of bile duct obstruction, manifested by high fever, chills and leucocytosis. Blood cultures are usually positive and liver biopsies show neutrophils in bile ducts and surrounding micro-abscesses. *E. coli* is the most common pathogen; the incidence in our series was 14%, in keeping with other reports of 3–15% *(1,4,7,13)*. In our view, the indications for operation are cholangitis and persistence of obstructive jaundice of 1 month's duration or more. In agreement with others, we would recommend such a period because in other conditions resolution would normally have taken place by then *(13)*. Another reason for operation is the possible development of anergy, reversible after relief of the obstruction *(14)*. Biliary–enteric bypass can be most expeditiously performed by means of a side-to-side choledochoduodenostomy. The anatomical and physiological arrangements make this the procedure of choice. A choledochojejunostomy Roux-en-Y requires an additional suture line and offers no substantial advantage in the absence of duodenal obstruction. Cholecystojejunostomy is a less reliable outflow tract, as the narrow cystic duct with its Heysterian valves is a bottleneck and the gallbladder wall is prone to inflammation and shrinkage, as demonstrated in two of our patients. Furthermore, a low entry of the cystic duct is common. Its use may, therefore, be more appropriate for malignant pancreatic disease with a short life expectancy. The routine removal of the gallbladder during choledochoenteric bypass is supported by the finding of a high incidence of cholecystitis in our series, presumably related to bile stasis and increased intraluminal pressure. A primary biliary bypass operation *per se* is

a low risk procedure. Mortality in our series was related to the need for revisional surgery, concomitant medical disease and exsanguinating pseudocyst-related haemorrhage. This last complication is fairly uncommon and operative exploration is an unrewarding task. An alternative approach by means of transcatheter selective arterial embolisation is worth trying *(15)*. In our series, none of the patients were diagnosed as having carcinoma of the pancreas head, neither at operation nor at available biopsies. During follow-up, no death occurred on the basis of carcinoma. Exclusion of pancreas carcinoma is not easy and diagnosis may be missed despite exploration and biopsy. In the preoperative investigations of patients with pancreatitis and jaundice ERCP plays a central role. It outlines disease in the biliary as well as the pancreatic ducts and helps to identify candidates for dual ductal drainage *(13,16–18)*. Intraoperative cholangiography is mandatory where ERCP has failed and PTC has not been performed, especially when a pseudocyst is present and alleged to be contributing to the obstruction. An underlying stricture of the CBD should be dealt with when bile is not seen to enter the duodenum freely after decompression of the cyst *(17)*.

In conclusion, fixed bile duct obstruction is not an uncommon complication of chronic pancreatitis and should be dealt with surgically if no improvement is noted after a period of observation. Duct-enteric bypass is most effective and choledochoduodenostomy the procedure of choice. ERCP or intraoperative pancreatography provide information as to whether concomitant pancreatic duct drainage may be indicated. Drainage of pseudocysts may relieve bile duct obstruction. If intraoperative cholangiography shows persistent obstruction after cyst drainage, duct-enteric bypass is also required.

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Assessors' comments

> . . . but if the passages which convey the bile to the intestine be obstructed by inflammation of scirrhus, the [gall] bladder gets overdistended, and the bile regurgitates . . . to every point of the body, which acquires the appearance of bile.
>
> *Aretaios* (*c* second century AD)

Although Riedel is considered to have provided the first report of obstructive jaundice in chronic pancreatitis in 1896 *(1)*, Aretaios, the Cappadocian, a prominent physician of the 'late Greek period' must be given some credit *(2)*. While Mayo-Robson in his series of Hunterian Lectures described successful surgical treatment *(3)*, it is